The opinion in support of the decision being entered today was *not* written for publication and is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte GUNARS E. VALKIRS, JEFFREY R. DAHLEN, HOWARD J. KIRCHICK, and KENNETH F. BUECHLER

Appeal 2007-0628
Application 10/225,082
Technology Center 1600

Decided: April 17, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and NANCY J. LINCK, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of diagnosing stroke, which the Examiner has rejected for lack of adequate description and obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

"Stroke can be categorized into two broad types, 'ischemic stroke' and 'hemorrhagic stroke'" (Specification 1). Ischemic stroke is caused by

inadequate blood flow to brain tissue, and hemorrhagic stroke is caused by a ruptured blood vessel in the brain (*id.* at 2). The different types of stroke require different treatments (*id.* at 3).

The Specification discloses that the two types of stroke can be distinguished from each other, and from transient ischemic attacks (TIAs), by assaying for certain proteins in the blood (*id.* at 4). More precisely, the Specification states that assaying for at least one specific marker of cerebral injury and at least one non-specific marker of cerebral injury provides a "rapid, sensitive and specific diagnostic assay to be used in the diagnosis and differentiation of various forms of stroke and TIAs" (*id.*).

Specific markers of cerebral injury are "polypeptides that are associated with brain tissue and neural cells, and which can be correlated with a cerebral injury, but are not correlated with other types of injury" (*id.* at 8:1-3). They include S100β (*id.* at 8:6). "[S]pecific markers of cerebral injury may . . . be found in the blood . . . as well as the CSF of a patient experiencing stroke or TIAs" (*id.* at 15:13-15). Non-specific markers of cerebral injury are "polypeptides that are elevated in the event of cerebral injury, but may also be elevated due to non-cerebral events," and include caspase-3 (*id.* at 8:10-11, 16).

DISCUSSION

1. CLAIMS

Claims 45, 47, 50, 53-69, 73, 75, 77, 80, 83-99, and 103 are on appeal. Claims 46, 48, 49, 51, 52, 70-72, 74, 76, 78, 79, 81, 82, 100-102, and 104 are also pending but have been withdrawn from consideration by the Examiner.

Claim 45 is representative and reads as follows:

A method of determining a diagnosis of stroke or cerebral injury in a subject, said method comprising:

analyzing a test sample obtained from a subject for the presence or amount of one or more markers selected from the group consisting of adenylate kinase, brain-derived neurotrophic factor, calbindin-D, creatine kinase-BB, glial fibrillary acidic protein, lactate dehydrogenase, myelin basic protein, neural cell adhesion molecule, neuron-specific enolase, neurotrophin-3, one or more isoforms of protein kinase C, proteolipid protein, S-100β, brain-derived neurotrophic factor, thrombomodulin, and marker(s) related thereto;

analyzing said test sample for the presence or amount of one or more markers selected from the group consisting of acute phase reactants, A-type natriuretic peptide, B-type natriuretic peptide, C-type natriuretic peptide, adrenomedullin, endothelin-1, endothelin-2, endothelin-3, β-thromboglobulin, cardiac troponin I, caspase-3, creatine kinase-MB, D-dimer, fibrinopeptide A, head activator, hemoglobin a_2 chain, interleukin-8, myoglobin, plasmin-a-2 antiplasmin complex, platelet factor 4, prothrombin fragment 1+2, thrombin-antithrombin III complex, tissue factor, vascular endothelial growth factor, one or more forms of von Willebrand factor, and marker(s) related thereto; and

correlating the presence or amount of the analyzed markers to the occurrence or nonoccurrence of a stroke or cerebral injury in said subject.

Claim 45 is directed to a method of diagnosing stroke or cerebral injury by analyzing a sample from a patient for at least two markers: one chosen from a set of specific markers of cerebral injury and one chosen from a set of non-specific markers of cerebral injury. The claim language reciting "analyzing a test sample . . . ; analyzing *said* test sample" indicates that the same test sample is used in both assays.

The claim also requires correlating the results of the assays to determine whether the subject has suffered a stroke or cerebral injury. The specification defines "correlating" to mean "comparing the presence or

amount of the indicator in a patient to its presence or amount in persons known to suffer from, or known to be at risk of, a given condition; or in persons known to be free of a given condition" (Specification 9).

Claim 45 is a "Markush-type" claim (see MPEP § 803.02). Thus, the Examiner requested an election-of-species. In response to that request, Appellants elected S100β as the specific marker of cerebral injury and caspase-3 as the non-specific marker of cerebral injury (Br. 8).[1]

2. WRITTEN DESCRIPTION

Claims 45, 47, 50, 53-69, and 73 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner focuses on the recitation in the claims, in addition to the specified protein markers, of "marker(s) related thereto." The Examiner notes that the Specification defines "related marker" to mean "fragments of a particular marker that may be detected as a surrogate for the marker itself" (Answer 5) but argues that that definition is an inadequate description because the specification does not define "what the fragments of S100β and caspase-3 are" (*id.*).

[1] Appellants have requested that, in the event that the rejections on appeal are reversed, the Board direct the Examiner to apply the procedures of the MPEP relating to restriction/election of Markush claims in future prosecution (Br. 4-5). We decline to do so. Restriction practice is a procedural matter that is normally reviewed by way of petition, not appeal. It is true that, in some cases, a restriction amounts to a de facto rejection and is properly appealable (*see, e.g., In re Haas*, 486 F.2d 1053, 179 USPQ 623 (CCPA 1973)), but it would be premature to decide whether this case is in that category.

Appellants argue that "the 'related markers' [are] all characterized by their structural relationship to a parent marker, the structure of which is well known" (Br. 12) and that "[a]s the proteins recited in the claims are all known proteins having known sequences, the identity of various 'related' polypeptides (e.g., the corresponding 'precursor' and 'NT-pro' forms) may be easily ascertained from . . . a standard database" (*id.* at 13-14).

We agree with Appellants that the Examiner has not shown that the "related markers" recited in the claims are not adequately described. The Examiner argues that the Specification's definition of related markers is "inclusive and nonlimiting and thus is not limited to fragments" (Answer 9). We disagree. "Related marker" is expressly defined to mean "fragments of a particular marker that may be detected as a surrogate for the marker itself" (Specification 5).

Appellants have asserted that all the proteins recited in the claims are known in the art, and the Examiner has not disputed that assertion. Thus, the "related markers" recited in the claims are merely fragments of known proteins. We agree with Appellants that the sequences of known proteins, and fragments of them, are readily available to those skilled in the art. "[T]here is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). "Indeed, [such a requirement], if one existed, would serve no goal of the written description requirement." *Id.* at 1368, 79 USPQ2d at 1008.

The Examiner has not established that the claims are unpatentable under 35 U.S.C. § 112, first paragraph. The rejection of claims 45, 47, 50, 53-69, and 73 for lack of adequate written description is reversed.

3. OBVIOUSNESS

All of the claims on appeal stand rejected under 35 U.S.C. § 103, as follows:

- Claims 45, 47, 50, 73, 75, 77, 80, and 103 as obvious in view of Martens[2] and Phanithi;[3]
- Claims 53-68 and 83-98 as obvious in view of Martens, Phanithi, and "further in view of appellants['] own disclosure;" and
- Claims 69 and 99 as obvious in view of Martens, Phanithi, and Jackowski.[4]

Since all of these rejections rely on the combination of Martens and Phanithi, we can consider them together.

The Examiner relies on Martens for its disclosure of assaying for S100β in cerebrospinal fluid (CSF) and its teaching that "S100β is elevated in CSF due to cerebral ischemia" (Answer 5). The Examiner also notes that Martens teaches that a second marker is elevated in CSF during cerebral ischemia, but does not teach assaying for caspase-3 (*id.*).

---

[2] Martens et al., "Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia," *Stroke*, Vol. 29, pp. 2363-2366 (1998).

[3] Phanithi et al., "Mild hypothermia mitigates post-ischemic neuronal death following focal cerebral ischemia in rat brain: Immunohistochemical study of Fas, caspase-3, and TUNEL," *Neuropathology*, Vol. 20, pp. 273-282 (2000).

[4] Jackowski, US 6,235,489, May 22, 2001.

The Examiner characterizes Phanithi as "teach[ing] that caspase-3 is elevated in cerebral ischemia" (*id.*), and concludes that

> [i]t would have been obvious . . . to also analyze the test sample of Martens et al for caspase-3 because Phanithi et al teaches that caspase-3 is elevated in cerebral ischemia and it would have been obvious to combine the two markers for the detection of cerebral ischemia because both markers are known to be elevated in cerebral ischemia and thus the detection of a second marker provides further confirmation of cerebral ischemia.

(*Id.* at 6.)

Appellants argue that

> the primary Martens *et al.* publication examines S100β levels in *serum and cerebrospinal fluid samples*, while the secondary Phanithi *et al.* publication detects cytoplasmic expression of caspase-3, an intracellular protein, in *histological sections of brain tissue*. . . . Nothing in either publication discloses or suggests that, in the case of stroke or cerebral injury, it is possible for S100β and caspase-3 to be measured in the same type of sample.

(Br. 17.) Appellants cite the second declaration of Kenneth F. Buechler, submitted May 11, 2005, as supporting their position.

We agree with Appellants that the Examiner has not made out a prima facie case of obviousness. As Appellants point out, Martens discloses that levels of S100β in *serum or CSF* were significantly higher in patients who never regained consciousness (Martens, p. 2364, col. 2) while Phanithi discloses that caspase-3 is expressed in *brain cells* after ischemia (p. 276, col. 2 ("Staining was cytoplasmic . . .")). Phanithi does not state that caspase-3 was found in CSF or serum. Nor does Phanithi provide any other basis for concluding that the caspase-3 detected by immunostaining would

be expected to be released from the cells in which it was expressed and be detectable in CSF or serum.

The Examiner argues that CSF is "a sample of the same type as brain tissue because CSF and brain tissues are within the same system in the body and one of ordinary skill in the art would expect markers which are known to be within the brain tissue would also . . . be contained within CSF" (Answer 12). The Examiner cites Vander,[5] Webster's,[6] and Jackowski as

> show[ing] that CSF and brain tissue clearly are within the same system in the body and particularly Jackowski shows that proteins that are released by brain cells during a cerebral event can be detected in cerebrospinal fluid. Thus, since the prior art teaches the equivalence of brain tissue and CSF as samples for markers related to cerebral ischemia. It would have been obvious to one of ordinary skill in the art at the time the invention was made to expect the markers which are known to be within the brain tissue to also be in CSF.

(*Id.* at 13.)

We do not agree with the Examiner's reading of the cited references. Webster's merely defines "tissue" as an "aggregation of morphologically and functionally similar cells"; it does not provide any basis for concluding that brain cells and CSF meet that definition. Vander teaches that CSF surrounds the brain, but does not teach that the contents of brain cells are found in CSF.

Jackowski is more relevant to the Examiner's argument, in that it teaches that myelin basic protein, S100, and neuron-specific enolase are "released by the specific brain cells as the cells become damaged during a

---

[5] Vander et al., *Human Physiology*, 6th ed., pp. 214-215, 230 (1994).
[6] Webster's II, New Riverside University Dictionary, p. 1212 (1994).

cerebral event" (col. 5, ll. 12-14). Jackowski teaches that all three proteins are found in CSF after release from brain cells (col. 5, ll. 34-37, 64-66; col. 6, ll. 19-22).

However, Jackowski teaches that S100β has about a two-hour half-life when released in serum (col. 5, ll. 61-62) and that its level in "fluid collected from brain," presumably CSF, peaked about 180 minutes after an ischemic event (col. 7, ll. 8-20). Phanithi, by contrast, teaches that caspase-3 was not detectable, even intracellularly, until three hours after reperfusion (p. 280, left-hand column).

If caspase-3 were detectable in CSF at all, it would only be after the cells expressing it had completed the apoptotic process, died, and released their cellular contents into the extracellular space. Phanithi teaches that the TUNEL detects cells undergoing apoptosis, that no TUNEL-positive cells were detected until five hours after reperfusion, and that the number of TUNEL-positive cells peaked twenty-four hours after reperfusion (page 280, paragraph bridging the columns). Phanithi does not suggest whether the apoptotic cells would release their contents into the CSF, or whether they would do so in a detectable amount, but it does suggest that, if they did, the release would be unlikely to coincide with the presence of S100β in CSF.

Finally, Härter[7] teaches that "the presence of active caspase-3 is a good indicator of apoptosis. To date it is unknown whether active caspase-3 can be released from cells dying by apoptosis into CSF" following traumatic

---

[7] Härter et al., "Caspase-3 activity is present in cerebrospinal fluid from patients with traumatic brain injury," *Journal of Neuroimmunology*, Vol. 121, pp. 76-78 (2001). Härter was cited on the Form PTO-892 mailed July 25, 2005.

brain injury. Härter, *supra*, at 76. Härter was published in December 2001, and therefore provides further evidence that those skilled in the art did not have an expectation of detecting caspase-3 in CSF as of the instant application's claimed effective filing date of August 20, 2001 (Specification 1).[8]

Thus, we conclude that the evidence of record does not adequately support the Examiner's position that the cited references would have made it obvious to obtain a single sample from a subject who may have suffered a stroke, and assay the same sample for both S100β and caspase-3. The rejection for obviousness is reversed.

SUMMARY

The Examiner has not shown that the claims on appeal are not adequately described in the specification or that the claimed method would have been obvious to a person of ordinary skill in the art. The rejections under 35 U.S.C. §§ 112, first paragraph, and 103 are reversed.

REVERSED

lbg

[8] The Examiner has provided no basis on which to conclude that the present claims are not entitled to priority based on provisional application 60/313,775, filed August 20, 2001.

FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO CA 92138-0278